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# Epidemiologic Study of Renal Function in Copper Smelter Workers

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**A medical cross-sectional examination of a copper smelter work force was undertaken after environmental contamination with lead, cadmium and arsenic had been documented. A total of 920 subjects was examined, including active smelter employees, retired workers and copper mine employees who had never worked in the smelter.**

**Slight to moderate absorption of lead and cadmium was definitely present in the active copper smelter employees, who had significantly higher levels of Pb-B, ZPP and Cd-B than retired employees and miners. Cd-U levels were higher in retired workers, who were also older and had, as a group, longer duration of exposure in the smelter. Cd-U did not exceed 10 μg/g creatinine, the level considered critical for nephrotoxicity, in any of the subjects. Median Cd-B level for active workers was 2.75 μg/L. Lead absorption was characterized by a relatively small proportion (16.7%) of active employees with Pb-B levels 40 μg/dL or higher.**

**We were particularly interested in exploring the possibility that simultaneous exposure to lead and cadmium, although at levels not associated with nephrotoxicity for each metal separately, could result in renal function impairment. Distribution patterns of BUN and serum creatinine levels were unremarkable. Urinary $\beta_2$-microglobulin levels were less than 200 μg/g creatinine in 95% of copper smelter employees. There were no significant correlations between urinary $\beta_2$-microglobulin levels and Cd-U, Cd-B, Pb-B and ZPP or between urinary $\beta_2$-microglobulin excretion and serum creatinine or BUN levels. Urinary $\beta_2$-microglobulin levels were significantly correlated with age in the copper smelter workers, but not in the miners. Nevertheless, in the absence of any significant correlations between urinary $\beta_2$-microglobulin and Cd-U, Cd-B, a causal relationship with cadmium absorption cannot be affirmed.**

**That kidney function could be impaired by long-term exposure in the smelter was only indirectly suggested. Effects on renal function at the low levels of cadmium and lead absorption that were observed in this smelter population are minimal.**

## Introduction

Lead, cadmium and arsenic emissions from a large copper smelter were found to result in environmental contamination and significant absorption in segments of the population living in the immediate vicinity of this copper smelter.

An increase in lead levels in blood (Pb-B) and hair (Pb-H) and a corresponding inhibition of aminolevulinic acid dehydratase (ALA-D) were found to be more prominent in school children; higher levels of cadmium and arsenic in hair were also present. Soil contamination through fallout from smelter emissions was found to be the major source. The higher Pb, Cd, and As levels in school children were thought to be the result of childhood activities (*1*). Blood lead levels were generally not found to exceed 40 μg/dL. However, a significant proportion (especially among children) had Pb-B levels higher than 30 μg/dL, the upper limit of acceptable Pb-B levels in children.

The copper smelter, operating since 1927, is known to generate monthly emissions of 110 tons of lead, 25 tons of arsenic, 13 tons of cadmium as well as large amounts of sulfur dioxide (*2*). With the information on environmental contamination documenting definite undue exposure to the population living around the smelter, the need for a

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**Table 1. Age distribution of copper smelter workers.**

| Age, yr | Smelter workers, Active N | % | Retired N | % | Miners N | % |
|---|---|---|---|---|---|---|
| ≤ 30 | 143 | 21.0 | 3 | 3.1 | 5 | 3.5 |
| 31–40 | 161 | 23.7 | 6 | 6.2 | 8 | 5.6 |
| 41–50 | 132 | 19.4 | 5 | 5.2 | 16 | 11.1 |
| 51–60 | 188 | 27.6 | 23 | 24.0 | 53 | 36.8 |
| > 60 | 56 | 8.2 | 59 | 61.4 | 62 | 43.1 |

comprehensive assessment of the health status of the employees was recognized.

## Populations and Methods

A cross-sectional medical examination of workers employed at this copper smelter was conducted. This included measurements of blood lead (Pb-B), blood zinc protoporphyrin (ZPP), blood cadmium (Cd-B), urinary cadmium (Cd-U) and urinary arsenic (As-U).

Lead and cadmium in blood were determined by graphite furnace atomic absorption spectrophotometry, using a Perkin-Elmer atomic spectrophotometer, Model 5000, with a 500 model graphite furnace (*3,4*). The detection limit for blood lead was 10 µg/L and the reproducibility ± 10%. The laboratory, Centre de Toxicologie du Québec, participates in the Center for Disease Control Analytical Proficiency Program for blood lead. The detection limit for blood cadmium was 0.2 µg/L with a precision of ± 5%. Graphite furnace atomic absorption spectrophotometry was also used for determination of cadmium and total arsenic in urine; the detection limit was 0.2 µg/L for urinary cadmium, and the precision was ± 5%. For urinary arsenic, the detection limit was 10 µg/L and the precision of the test ± 10%. A calibration curve was prepared by adding As to a pool of urine to yield concentrations between 0 and 200 µg/L. ZPP in blood was determined on capillary blood samples obtained by finger puncture by utilizing a hematofluorometer (Aviv Associates) (*5–7*).

Life-long occupational history, past medical history and symptoms elicited through review of symptoms questionnaire were recorded. Physical examination, clinical biochemistry, measurement of urinary $\beta_2$-microglobulin excretion by radioimmunoassay using the Phadebas $\beta_2$-micro test (Pharmacia Diagnostics) (*8*), chest X-ray film, and pulmonary function tests were also performed. Evaluation of the nervous system included neurobehavioral performance tests, nerve conduction velocity measurements and oculomotor function studies.

The examined population comprised 680 active smelter employees, 96 retired smelter employees (or ex-smelter employees) and 144 men who had never been employed in the smelter itself, but had worked as miners in copper and gold mines in the area. (The company had, until recently, operated its own copper mine.) Age distribution and duration of copper smelter employment are presented in Tables 1 and 2. More than half of the active workers had been employed for over 10 years.

By using information from industrial hygiene studies of copper smelters (*9*) the various job designations in the smelter were classified with regard to potential exposure to Pb, Cd and As into four categories: minimal, low, medium and high. The mobility of employees through several job categories was recognized, especially for those with long-term employment; an "equalization" effect was therefore possible. For certain parameters, when recent exposure was thought to be of special relevance, analysis according to current job assignment was undertaken.

The report presents results of the analysis of extensive data sets; numerous tables and figures are used to abstract this information. The probability that a specific (statistical) test will be significant by chance alone when such a vast collection of data is analyzed should be and was considered. As a result, we have attached little (physiological) significance to probability levels

**Table 2. Distribution of duration of copper smelter employment.**

| Duration, yr | Duration of copper smelter employment: Active workers (N = 680) N | % | Retirees (N = 96) N | % | Duration from onset of copper smelter employment: Active workers (N = 680) N | % | Retirees (N = 96) N | % |
|---|---|---|---|---|---|---|---|---|
| < 5 | 178 | 26.2 | 20 | 20.8 | 167 | 18.7 | 11 | 11.5 |
| 5–9.9 | 151 | 22.2 | 10 | 10.4 | 151 | 22.2 | 5 | 5.2 |
| 10–19.9 | 197 | 29.0 | 20 | 20.8 | 209 | 30.7 | 15 | 15.6 |
| 20–29.9 | 119 | 17.5 | 21 | 21.9 | 132 | 19.4 | 19 | 19.8 |
| ≥ 30.0 | 35 | 5.1 | 25 | 26.0 | 61 | 9.0 | 46 | 47.9 |

less than 0.001. Where an association is discussed, the probability levels are often in the 0.00001 range.

It is also well known that the proportion of the total variance of $s_Y^2$ (the variance of the dependent variable) associated with a variation in $X$ is equal to $r^2$. Therefore, a correlation coefficient can be significant and the value of $r^2$ be low. Values of $r^2$ (coefficients of determination) were always taken into consideration, although not reported because this simply involves squaring the magnitude of the correlation coefficient ($r$).

Partial correlations were computed by the formula:

$$r_{12.3} = \frac{r_{12}r_{13}r_{23}}{\sqrt{(1 - r_{13}^2)(1 - r_{23}^2)}}$$

where $r_{12.3}$ indicates the partial correlation coefficient between variables 1 and 2 in a number of individuals, all having the same value of variable 3. Partial correlations were used to explore the relationship between hypertension and urinary cadmium, controlling for age, and creatinine and urinary cadmium, controlling for age. Multiregression analyses were performed by using computer algorithms, especially the "best subset" regression which calculates both the $r^2$ and Mallows' $C_p$ statistics. Further details of the use of these techniques can be found in Draper and Smith (*10*).

Parametric versus nonparametric tests were used according to the following rationale. Each continuous variable was tested for normality and logarithmic transformations were used if and when such transformations improved the normality of the distribution. The criterion for normality was the probability value associated with $D$ in the Kolmogorov–Smirnov test. If a variable was found to be normally distributed, appropriate statistical tests based on bell-shaped distributions were used (Pearson's $r$); otherwise, nonparametric techniques were applied (Spearman's $r$).

Categorical data (yes–no type) were analyzed by statistical methods underlying the assumptions of the chi-square tests.

## Results

Mean Pb-B, ZPP and Cd-B were significantly higher in active copper smelter employees than in retirees or miners (Tables 3–5), indicating exposure and absorption in the copper smelter. Significant correlations between Pb-B and Cd-B and between Pb-B and Cd-U were present (Figs. 1 and 2), confirming the common source of absorption. Cd-B and Cd-U were significantly correlated for active and retired copper smelter employees (Figs. 3 and 4). Although there was evidence for an increased lead absorption, this was very moderate, with practically no Pb-B levels in excess of 60 µg/dL.

A marked effect of smoking on blood cadmium levels was present (Fig. 5); nevertheless, for all smoking categories Cd-B levels were significantly higher in active employees (Table 6), indicating the independent contribution of exposure to cadmium in the smelter. The effect of smoking on Pb-B was not significant (Table 7).

Recently reported Cd-B levels in samples of the general population (*11*) in ten countries indicate for U.S. males a geometric mean for nonsmokers of 0.6 µg/L and for smokers 1.2 µg/L. Thus, Cd-B levels in active copper smelter workers were higher than those reported for U.S. males, including smokers.

Cd-U did not exceed 10 µg/g creatinine, the generally accepted "critical" level for the kidney, but was higher than 2 µg/g creatinine (Table 8) in 12.6% of active and 25% of retired smelter em-

**Table 3. Distribution, median and mean values of blood lead levels (Pb-B).**

| Pb-B, µg/dL | Active smelter workers ($N$ = 680) $N$ | % | | Retirees ($N$ = 96) $N$ | % | | Miners ($N$ = 144) $N$ | % |
|---|---|---|---|---|---|---|---|---|
| < 40 | 566 | 83.2 | | 94 | 97.9 | | 141 | 97.9 |
| 40–59 | 111 | 16.3 | | 2 | 2.1 | | 3 | 2.1 |
| 60–79 | 3 | 0.4 | | 0 | — | | 0 | — |
| Median | 30.4 | | | 19.5 | | | 17.4 | |
| Mean ± SD | 31.1 ± 9.69 | | | 20.2 ± 6.62 | | | 19.2 ± 7.07 | |
| $t$ | | | 14.1 $p < 0.0001$ | | | 1.15 n.s. | | |
| $t$ | | | | 17.1 $p < 0.00001$ | | | | |

**Table 4. Distribution, median and mean values of zinc protoporphyrine (ZPP) levels in copper smelter employees.**

| ZPP, µg/dL | Active employees (N = 671) | | | Retirees (N = 96) | | | Miners (N = 144) | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | | N | % | | N | % | |
| < 50 | 180 | 26.8 | | 34 | 35.4 | | 47 | 32.6 | |
| 50–99 | 379 | 56.5 | | 56 | 58.3 | | 91 | 63.2 | |
| 100–199 | 97 | 14.5 | 16.7% | 4 | 4.2 | 6.3% | 5 | 3.5 | 4.2% |
| ≥ 200 | 15 | 2.2 | | 2 | 2.1 | | 1 | 0.7 | |
| Median | 41.5 | | | 36.2 | | | 37.0 | | |
| Mean ± SD | 49.6 ± 26.8 | | | 42.2 ± 20.4 | | | 39.9 ± 16.5 | | |
| $t$ | | | 3.18 | | | 0.93 | | | |
| | | | $p = 0.002$ | | | n.s. | | | |
| $t$ | | | | 5.65 | | | | | |
| | | | | $p = 0.0001$ | | | | | |

**Table 5. Distribution, median and mean values of blood cadmium levels in copper smelter employees.**

| Cd-B, µg/L | Active employees (N = 680) | | | Retirees (N = 96) | | | Miners (N = 144) | |
|---|---|---|---|---|---|---|---|---|
| | N | % | | N | % | | N | % |
| < 5.0 | 426 | 62.7 | | 68 | 70.8 | | 108 | 75.0 |
| 5.0–10.0 | 176 | 25.9 | | 23 | 24.0 | | 29 | 20.1 |
| 11.0–20.0 | 75 | 11.0 | | 5 | 5.2 | | 6 | 4.2 |
| > 20.0 | 3 | 0.4 | | 0 | — | | 1 | 0.7 |
| Median | 2.75 | | | 1.70 | | | 1.80 | |
| Mean ± SD | 4.46 ± 4.25 | | | 3.46 ± 3.45 | | | 3.30 ± 2.53 | |
| $t$ | | | 2.27 | | | 0.35 | | |
| | | | $p = 0.01$ | | | n.s. | | |
| $t$ | | | | 3.44 | | | | |
| | | | | $p = 0.0007$ | | | | |

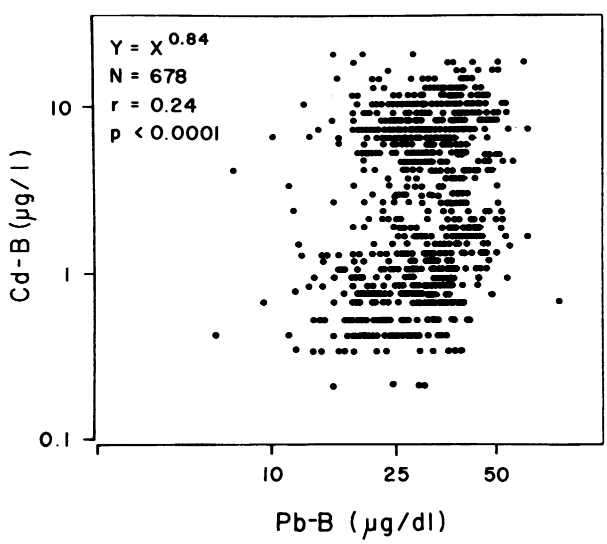


FIGURE 1. Relationship between blood lead (Pb-B) and blood cadmium (Cd-B) in active copper smelter employees.

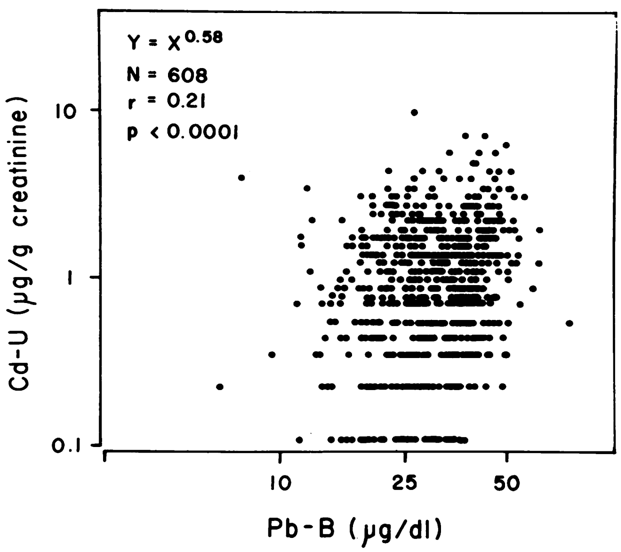


FIGURE 2. Relationship between blood lead (Pb-B) and urinary cadmium (Cd-U) in active copper smelter workers.

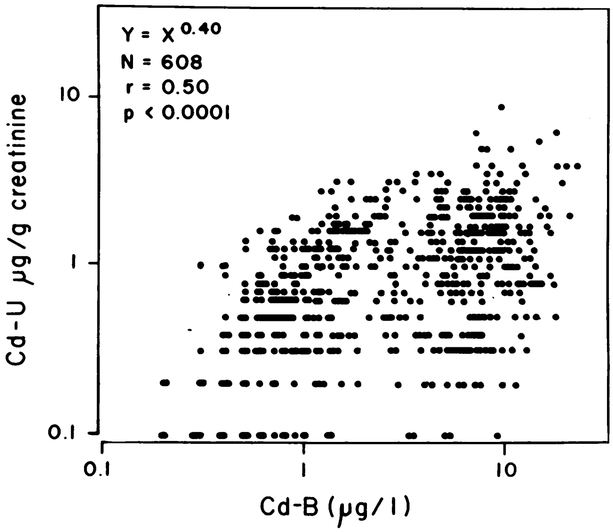


FIGURE 3. Relationship between blood cadmium (Cd-B) and urinary cadmium (Cd-U µg/g creatinine) in active copper smelter employees.

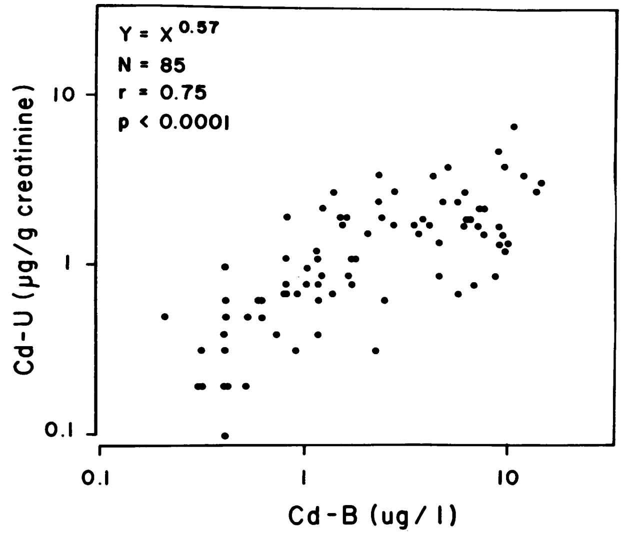


FIGURE 4. Relationship between blood cadmium (Cd-B) and urinary cadmium (Cd-U) in retired copper smelter employees.

**Table 6. Blood cadmium and smoking habits (mean ± SD).**

| | Blood Cd, µg/L | | | |
|---|---|---|---|---|
| | Smokers | Never smoked | *t* | *p* |
| Active smelter employees | 6.93 ± 4.10 | 1.04 ± 0.96 | 25.9 | < 0.0001 |
| Miners | 5.56 ± 3.64 | 0.57 ± 0.38 | 11.5 | < 0.0001 |
| *t* | 2.66 | 3.97 | | |
| *p* | 0.008 | 0.0002 | | |

**Table 7. Blood lead levels and smoking habits.**

| | Pb-B, µg/dL | | | | |
|---|---|---|---|---|---|
| | Smokers | | Nonsmokers | | |
| | *N* | Mean ± SD | *N* | Mean ± SD | *t* |
| Active smelter employees | 381 | 31.7 ± 9.5 | 121 | 30.7 ± 9.8 | 0.98 n.s. |
| Miners | 73 | 20.5 ± 8.0 | 21 | 18.7 ± 8.4 | 0.86 n.s. |
| *t* | | 9.44 | | 5.27 | |
| *p* | | 0.0001 | | 0.0001 | |

**Table 8. Distribution, median and mean values of urinary cadmium levels in copper smelter employees.**

| Cd-U, µg/g creatinine | Active employees (*N* = 680) | | | Retirees (*N* = 96) | | | Miners (*N* = 144) | |
|---|---|---|---|---|---|---|---|---|
| | *N* | % | | *N* | % | | *N* | % |
| <1 | 415 | 61.0 | | 50 | 52.1 | | 81 | 56.2 |
| 1–1.9 | 179 | 26.3 | | 22 | 22.9 | | 38 | 26.4 |
| 2–2.9 | 56 | 8.2 | | 15 | 15.6 | | 14 | 9.7 |
| 3–3.9 | 18 | 2.6 | | 6 | 6.2 | | 8 | 5.6 |
| 4–4.9 | 6 | 0.9 | | 2 | 2.1 | | 3 | 2.1 |
| 5–10 | 6 | 0.9 | | 1 | 1.0 | | 0 | — |
| Median | 0.90 | | | 1.10 | | | 1.00 | |
| Mean ± SD | 1.16 ± 1.03 | | | 1.52 ± 1.23 | | | 1.30 ± 1.08 | |
| *t* | | | 2.60 *p* = 0.01 | | | 1.40 n.s. | | |
| *t* | | | | 1.38 n.s. | | | | |

**Table 9. Blood cadmium levels, intensity of exposure and smoking habits in active copper smelter employees.**

| | | Cd-B in various exposure categories, μg/L | | | |
|---|---|---|---|---|---|
| | | Very low | Low | Medium | High |
| Smokers | $N$ | 48 | 102 | 103 | 128 |
| | Median | 5.03 | 6.75 | 7.10 | 6.90 |
| | Mean ± SD | 5.50 ± 4.07 | 6.79 ± 4.19 | 7.05 ± 3.66 | 7.48 ± 4.28 |
| Ex-smokers | $N$ | 21 | 55 | 52 | 47 |
| | Median | 0.70 | 0.90 | 1.00 | 1.40 |
| | Mean ± SD | 0.76 ± 0.34 | 1.03 ± 0.62 | 1.53 ± 1.80 | 1.02 ± 1.61 |
| Nonsmokers | $N$ | 11 | 35 | 33 | 42 |
| | Median | 0.50 | 0.60 | 0.80 | 1.00 |
| | Mean ± SD | 0.56 ± 0.27 | 0.65 ± 0.80 | 0.99 ± 0.80 | 1.53 ± 1.28 |

**Table 10. Urinary cadmium, intensity of exposure and smoking habits in active copper smelter employees.**

| | | Cd-U in various exposure categories, μg/g creatinine | | | |
|---|---|---|---|---|---|
| | | Very low | Low | Medium | High |
| Smokers | $N$ | 45 | 86 | 87 | 120 |
| | Median | 1.00 | 1.10 | 1.20 | 1.40 |
| | Mean ± SD | 1.23 ± 0.89 | 1.21 ± 0.89 | 1.45 ± 1.26 | 1.65 ± 1.33 |
| Ex-smokers | $N$ | 19 | 45 | 48 | 45 |
| | Median | 0.50 | 0.70 | 0.70 | 1.10 |
| | Mean ± SD | 0.69 ± 0.55 | 0.98 ± 0.81 | 0.88 ± 0.65 | 1.20 ± 0.81 |
| Nonsmokers | $N$ | 10 | 33 | 29 | 41 |
| | Median | 0.45 | 0.30 | 0.40 | 0.60 |
| | Mean ± SD | 0.50 ± 0.28 | 0.41 ± 0.27 | 0.62 ± 0.66 | 0.72 ± 0.47 |

**Table 11. Blood lead (median, mean ± SD, and range) in different job categories of copper smelter employees.**

| | | Pb-B, μg/dL | | |
|---|---|---|---|---|
| Job category | $N$ | Median | Mean ± SD | Range |
| Railroad construction yard | 24 | 22.1 | 23.0 ± 8.0 | 11.8–51.3 |
| Concentrator | 25 | 23.2 | 23.6 ± 4.2 | 15.2–31.9 |
| Laborer (outside) | 21 | 24.5 | 25.5 ± 8.3 | 11.8–41.3 |
| Carpenter | 22 | 25.0 | 26.3 ± 11.3 | 10.2–53.4 |
| Power house boiler | 15 | 25.2 | 25.2 ± 5.7 | 18.2–36.4 |
| Electrical shop | 36 | 25.3 | 25.3 ± 7.8 | 11.0–46.0 |
| Machine shop | 28 | 25.6 | 24.5 ± 6.5 | 12.1–38.1 |
| Roaster or mixer | 16 | 28.2 | 28.1 ± 9.4 | 12.1–43.6 |
| Welder | 18 | 28.9 | 32.8 ± 10.7 | 19.7–49.3 |
| Heavy equipment maintenance | 46 | 29.0 | 28.9 ± 10.0 | 7.9–50.0 |
| Pipefitter or plumber | 23 | 29.6 | 31.4 ± 10.0 | 16.5–52.9 |
| Concentrator unloading shed | 26 | 30.0 | 32.0 ± 9.2 | 15.2–51.9 |
| Sample mill | 32 | 31.2 | 28.5 ± 9.0 | 11.4–40.9 |
| Convertor | 72 | 31.3 | 30.7 ± 10.6 | 12.1–62.3 |
| Furnace | 84 | 32.5 | 32.4 ± 10.7 | 9.5–74.8 |
| Dust collector | 20 | 36.1 | 34.9 ± 10.2 | 18.9–53.6 |
| Reactor feeder | 47 | 38.3 | 37.2 ± 9.3 | 14.4–55.1 |
| Rigger | 27 | 39.6 | 39.4 ± 10.9 | 11.8–62.3 |

ployees. Such levels are uncommon in the absence of significant exposure (*12–14*). The highest Cd-U levels were found in retired copper smelter employees; age might have been a contributing factor, beside longer duration of exposure in the smelter.

There was a consistent increase in Cd-B and Cd-U according to increasing intensity of exposure (Tables 9 and 10; this occurred for all three smoking categories (smokers, ex-smokers, nonsmokers).

Mean, median and range of Pb-B, Cd-B and Cd-U in the most important occupations in the copper smelter are presented in Tables 11–13. The differences among the various occupations are obvious; for each of the metals, a subpopulation with higher absorption can be identified. The complex and relatively higher exposures to lead, cadmium and arsenic for some of the work assignments in this copper smelter raise the problem of potential health effects. Renal toxicity was of major concern, although neither lead nor cadmium absorption was in the range where nephrotoxicity is frequently found. The concomitant exposure and absorption of two nephrotoxic agents could nevertheless have resulted in adverse effects on renal function, even at relatively lower levels of absorption.

Excessive cadmium absorption has been associated with nephropathy characterized by an increase in the excretion of low molecular weight proteins (typically $\beta_2$-microglobulin), due to renal tubular dysfunction. Impairment of the proximal tubular segment of the nephron prevents the normal reabsorption of low molecular weight proteins from the glomerular filtrate. More recently, impairment of glomerular function has also been detected with reduction of glomerular filtration rate and an increase in serum creatinine (*15*).

Renal function in this study group was evaluated by blood urea nitrogen (BUN), serum creatinine, and uric acid measurements; urinary excretion of $\beta_2$-microglobulin was also assessed. Distribution of BUN levels in copper smelter employees was unremarkable (Table 14), with relatively few (3.4%) elevated values (BUN higher than 26 mg/dL). A similar pattern was found for serum creatinine (Table 15); levels of 1.4 mg/dL or higher were found in 3.6% of those examined.

Creatinine has not been found to correlate with age in populations without exposure to nephrotoxic agents (*16,17*). In some previous studies of lead-exposed groups (*18,19*), significant, positive correlations between serum creatinine, duration of lead exposure, and age were repeatedly found; the degree of these correlations was higher in occupational groups with higher levels of lead absorption. In the present study of copper smelter employees, significant correlations between se-

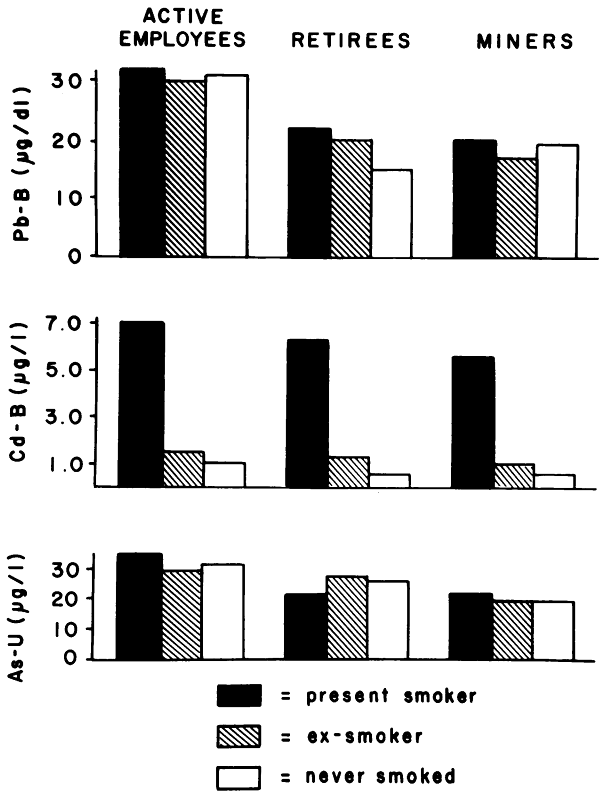


FIGURE 5. Smoking habits and Pb-B, Cd-B and As-U (mean values) in copper smelter employees.

**Table 12. Blood cadmium (median, mean ± SD and range) in different job categories of copper smelter employees.**

| | | Cd-B, µg/L | | |
|---|---|---|---|---|
| Job category | *N* | Median | Mean ± SD | Range |
| Machine shop | 28 | 1.10 | 2.96 ± 3.66 | 0.3–15.5 |
| Electrical shop | 36 | 1.20 | 2.61 ± 3.00 | 0.4–11.3 |
| Laborer (outside) | 21 | 1.40 | 2.82 ± 2.69 | 0.5– 9.5 |
| Railroad construction yard | 24 | 1.50 | 3.62 ± 4.21 | 0.3–13.5 |
| Convertor | 72 | 1.60 | 3.80 ± 3.72 | 0.3–14.3 |
| Carpenter | 22 | 1.65 | 3.22 ± 3.17 | 0.3– 9.1 |
| Pipefitter or plumber | 23 | 2.50 | 4.00 ± 3.81 | 0.4–12.3 |
| Furnace | 84 | 2.60 | 4.33 ± 4.15 | 0.1–18.1 |
| Sample mill | 32 | 3.35 | 5.35 ± 5.38 | 0.2–21.0 |
| Welder | 18 | 3.45 | 4.41 ± 3.60 | 1.0–14.7 |
| Heavy equipment maintenance | 46 | 3.50 | 4.35 ± 3.89 | 0.4–16.4 |
| Roaster or mixer | 16 | 4.00 | 4.67 ± 3.84 | 0.2–13.1 |
| Concentrator unloading shed | 26 | 4.20 | 5.69 ± 4.79 | 0.3–16.8 |
| Reactor feeder | 47 | 4.50 | 6.17 ± 4.68 | 0.4–18.6 |
| Concentrator | 25 | 4.70 | 4.84 ± 4.96 | 0.2–19.4 |
| Rigger | 27 | 5.20 | 5.29 ± 4.23 | 1.0–18.0 |
| Dust collector | 20 | 5.60 | 5.31 ± 3.71 | 0.4–11.4 |
| Power house boiler | 15 | 6.90 | 5.98 ± 4.66 | 0.4–13.4 |

**Table 13. Urinary cadmium, creatinine corrected (median, mean ± SD and range) in different job categories of copper smelter employees.**

| | | Cd-U, μg/g creatinine | | |
|---|---|---|---|---|
| Job category | *N* | Median | Mean ± SD | Range |
| Sample mill | 25 | 0.50 | 0.92 ± 0.74 | 0.1–2.4 |
| Electrical shop | 34 | 0.55 | 0.70 ± 0.55 | 0.1–1.9 |
| Railroad construction yard | 21 | 0.70 | 0.88 ± 0.61 | 0.3–2.4 |
| Concentrator | 16 | 0.70 | 0.99 ± 0.80 | 0.1–2.6 |
| Carpenter | 21 | 0.70 | 1.25 ± 1.27 | 0.1–5.0 |
| Power house boiler | 15 | 0.80 | 0.97 ± 0.73 | 0.2–2.8 |
| Machine shop | 26 | 0.80 | 1.12 ± 0.79 | 0.2–3.3 |
| Pipefitter or plumber | 19 | 0.80 | 1.09 ± 0.83 | 0.2–2.6 |
| Convertor | 64 | 0.90 | 1.08 ± 1.25 | 0.1–9.4 |
| Laborer (outside) | 19 | 1.00 | 1.10 ± 0.78 | 0.1–2.9 |
| Dust collector | 18 | 1.05 | 1.33 ± 1.26 | 0.2–4.9 |
| Rigger | 25 | 1.10 | 1.13 ± 0.81 | 0.2–3.7 |
| Heavy equipment maintenance | 44 | 1.10 | 1.34 ± 0.95 | 0.2–4.4 |
| Welder | 14 | 1.10 | 1.32 ± 1.13 | 0.1–4.2 |
| Concentrator unloading shed | 26 | 1.20 | 1.20 ± 0.77 | 0.1–2.9 |
| Roaster or mixer | 16 | 1.20 | 1.39 ± 1.05 | 0.2–3.8 |
| Reactor feeder | 42 | 1.20 | 1.61 ± 1.28 | 0.2–5.3 |
| Furnace | 81 | 1.40 | 1.65 ± 1.51 | 0.1–6.8 |

**Table 14. Blood urea nitrogen in copper smelter employees and miners.**

| | Copper smelter employees | | | | | |
|---|---|---|---|---|---|---|
| | Active ($N=602$) | | Retired ($N=72$) | | Miners ($N=117$) | |
| Blood urea nitrogen, mg/dL | *N* | % | *N* | % | *N* | % |
| < 24 | 546 | 90.7 | 60 | 83.3 | 97 | 82.9 |
| 24–26 | 38 | 6.3 | 7 | 9.7 | 7 | 6.0 |
| > 26 | 18 | 3.0 | 5 | 6.9 | 13 | 11.1 |

**Table 15. Serum creatinine in copper smelter employees and miners.**

| | Copper smelter employees | | | | | |
|---|---|---|---|---|---|---|
| | Active ($N=677$) | | Retired ($N=95$) | | Miners ($N=142$) | |
| Creatinine, mg/dL | *N* | % | *N* | % | *N* | % |
| < 1.3 | 630 | 93.1 | 86 | 90.5 | 119 | 83.8 |
| 1.3–1.39 | 25 | 3.7 | 2 | 2.1 | 9 | 6.3 |
| ≥ 1.4 | 22 | 3.3 | 7 | 7.4 | 14 | 9.9 |

rum creatinine and age, duration of employment and urinary cadmium were found (Table 16, Fig. 6). Cd-U was significantly correlated with age in copper smelter employees ($r = 0.455, p < 0.0001$); in miners no significant correlation between Cd-U and age was found ($r = -0.012$, n.s.). A partial correlation analysis of serum creatinine versus Cd-U in copper smelter employees, controlling for age, revealed that age accounted for the correlations between serum creatinine and Cd-U.

Distribution of urinary $\beta_2$-microglobulin levels (Table 17) indicated only a relatively small proportion of copper smelter workers with levels in excess of 200 μg/L; the distribution pattern did not differ from that of miners. Means, standard deviations, medians and ranges for urinary $\beta_2$-microglobulin levels are presented in Table 18. Cases with clinically established chronic renal conditions, hypertension and/or diabetes were excluded from the analysis.

The possible relationships between urinary $\beta_2$-microglobulin levels and Cd-U, Cd-B, Pb-B and ZPP were explored. No significant correlations were detected in either copper smelter employees

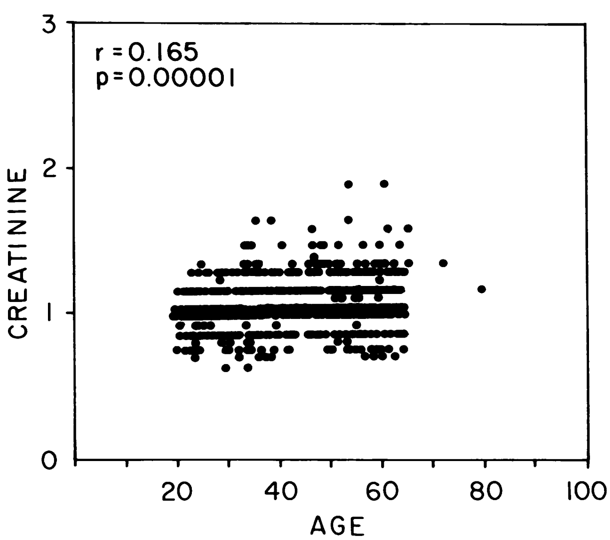


FIGURE 6. Relationship between serum creatinine and age in copper smelter workers ($Y = 0.99 + 0.0024X$).

**Table 16. Correlations between serum creatinine and age, duration of smelter employment and urinary cadmium in active smelter employees.**

| | Age, yr | Duration of smelter employment | Cd-U (density-corrected) |
|---|---|---|---|
| Creatinine, mg/dL | $r = 0.165$ <br> $p = 0.00001$ | $r = 0.131$ <br> $p = 0.0003$ | $r = 0.113$ <br> $p = 0.0054$ |

**Table 17. Urinary $\beta_2$-microglobulin levels in copper smelter employees and miners.**

| $\beta_2$-microglobulins, µg/g creatinine | Copper smelter employees ($N$=773) | | Miners ($N$=140) | |
|---|---|---|---|---|
| | $N$ | % | $N$ | % |
| < 200 | 734 | 95.0 | 129 | 92.2 |
| 200–399 | 30 | 3.9 | 8 | 5.7 |
| 400–999 | 8 | 1.0 | 2 | 1.4 |
| ≥ 1000 | 1 | 0.1 | 1 | 0.7 |

or miners. There were no significant correlations between urinary $\beta_2$-microglobulin excretion and serum creatinine or BUN levels.

Urinary $\beta_2$-microglobulin levels correlated significantly with age in copper smelter employees, but not in miners (Table 19, Figs. 7 and 8). The possibility that long-term exposure in the copper smelter might result in higher levels of $\beta_2$-microglobulin cannot be completely excluded. Although age has been found in other studies (*20*) to be associated with urinary $\beta_2$-microglobulin levels, such a relationship was not found for the miners in this study. Among the active copper smelter workers, a younger group than the miners, a highly significant correlation between urinary $\beta_2$-microglobulin excretion and age was present which may indicate an effect of the smelter environment. Nevertheless, in the absence of any significant correlations between urinary excretion of $\beta_2$-microglobulin and Cd-U, Cd-B, the causal relationship with increased cadmium absorption cannot be affirmed.

The results of the analysis of renal function (BUN, serum creatinine, and urinary $\beta_2$-microglobulin) in this group of copper smelter employees indicate only indirectly that kidney function could be impaired by long-term exposure in the smelter. The relevant findings are limited to a significant correlation between serum creatinine and age (a relationship not present in populations not exposed to nephrotoxic agents), and a significant correlation between urinary $\beta_2$-microglobulin levels and age, present in copper smelter workers, but not found in miners.

The renal effects of cadmium and lead in this population of copper smelter workers were clinically less evident than those reported for other cadmium-exposed occupational groups (*15*) or those found by us in lead-exposed groups (*18,19*).

**Table 18. Urinary $\beta_2$-microglobulin levels ($\beta_2$-M) in copper smelter employees and miners.**

| | Copper smelter employees | | | | | |
|---|---|---|---|---|---|---|
| | Active ($N$=560) | | Retired ($N$=78) | | Miners ($N$=113) | |
| Urinary $\beta_2$-microglobulins | $\beta_2$-M, µg/L (density corrected) | $\beta_2$-M, µg/g (creatinine corrected) | $\beta_2$-M, µg/L (density corrected) | $\beta_2$-M, µg/g (creatinine corrected) | $\beta_2$-M, µg/L (density corrected) | $\beta_2$-M, µg/g (creatinine corrected) |
| Mean | 122.8 | 82.0 | 127.4 | 88.1 | 156.1 | 106.8 |
| Standard deviation | 119.5 | 103.7 | 117.5 | 84.9 | 187.7 | 141.6 |
| Median | 97 | 63 | 93.5 | 67 | 116 | 72 |
| Range | 3–1135 | 2–1760 | 8–740 | 6–491 | 6–1270 | 3–1061 |

**Table 19. Correlations between urinary $\beta_2$-microglobulin levels and age in copper smelter employees and miners.**

| | Age | |
|---|---|---|
| | Copper smelter employees | Miners |
| Urinary $\beta_2$-M (log transformed) | $r = 0.119$ <br> $p = 0.002$ | $r = -0.109$ <br> $r = -0.109$ n.s. |

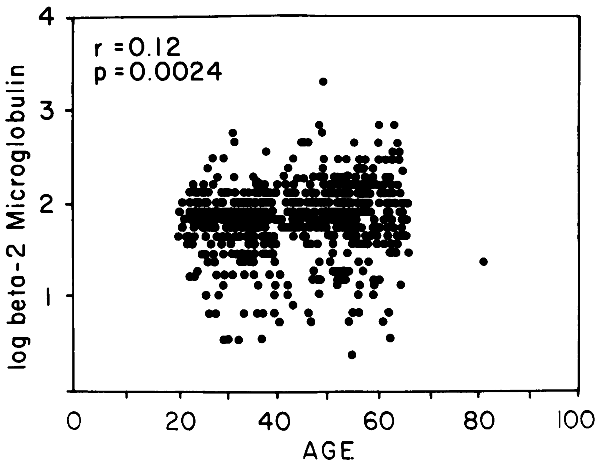


FIGURE 7. Relationship between urinary $\beta_2$-microglobulin (logarithmic transformation) and age in copper smelter employees.

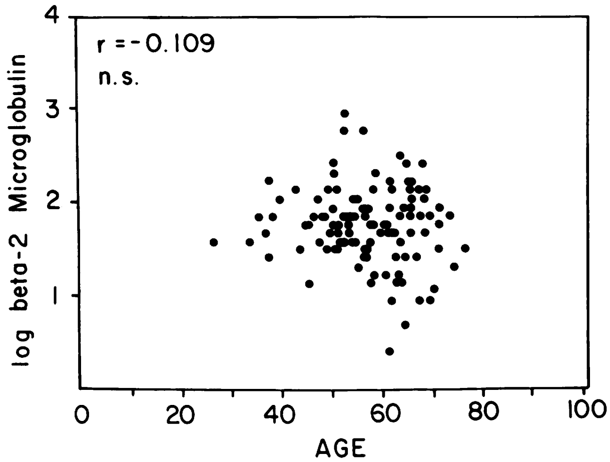


FIGURE 8. Relationship between urinary $\beta_2$-microglobulin (logarithmic transformation) and age in miners.

The results of the present study indicate that effects on renal function at the low levels of cadmium and lead absorption that were observed in this smelter population were minimal.

Hypertension was also of special interest, since both lead and cadmium have been considered to be potentially related to hypertension. In a previous study of an occupationally lead-exposed group (automobile assembly body shop workers) significantly higher diastolic blood pressure than in a comparison group without lead exposure was documented (*19*). Although the level of lead absorption in the present study group—as reflected in Pb-B and ZPP levels—is lower than that among auto body workers, the copper smelter employees are also exposed to cadmium. There-

**Table 20. Prevalence of hypertension (systolic > 150 mm Hg, diastolic > 95 mm Hg) in copper smelter employees and in miners.**

| | Copper smelter employees | | | | | Miners | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Systolic > 150 mm Hg | | Diastolic > 95 mm Hg | | | Systolic > 150 mm Hg | | Diastolic > 95 mm Hg | |
| Age, yr | Total *N* | *N* | % | *N* | % | Total *N* | *N* | % | *N* | % |
| <30 | 131 | 6 | 4.6 | 4 | 3.0 | 4 | 0 | — | 0 | — |
| 30–50 | 319 | 24 | 7.5 | 23 | 7.2 | 25 | 2 | 8.0 | 3 | 12.0 |
| >50 | 326 | 97 | 29.7 | 49 | 15.0 | 115 | 38 | 33.0 | 21 | 18.3 |

**Table 21. Correlations between blood pressure (systolic and diastolic), age and urinary cadmium excretion in copper smelter employees and miners.**

| | Copper smelter employees: Total (active and retired), Blood pressure | | Copper smelter employees: Active employees only, Blood pressure | | Miners, Blood pressure | |
|---|---|---|---|---|---|---|
| | Systolic | Diastolic | Systolic | Diastolic | Systolic | Diastolic |
| Age | | | | | | |
| *r* | 0.411 | 0.288 | 0.376 | 0.280 | 0.346 | 0.179 |
| *p* | < 0.000001 | < 0.000001 | < 0.000001 | <0.000001 | 0.00001 | 0.016 |
| CdU, μg/g creatinine | | | | | | |
| *r* | 0.145 | 0.075 | 0.151 | 0.105 | −0.119 | −0.114 |
| *p* | 0.00006 | 0.025 | < 0.000001 | 0.0048 | 0.092 (n.s.) | 0.102 (n.s.) |
| log Cd-U | | | | | | |
| *r* | 0.150 | 0.094 | 0.148 | 0.123 | −0.082 | −0.09 |
| *p* | 0.00004 | 0.007 | < 0.00013 | 0.001 | 0.182 (n.s.) | 0.158 (n.s.) |

fore, the possibility that hypertension could occur with higher frequency was investigated.

Prevalence rates for hypertension (systolic and diastolic) in copper smelter employees and miners, by age group, are presented in Table 20. No significant differences were found between copper smelter employees and miners in any of the age categories. Only in the age group over 50 yr was diastolic hypertension found with a higher prevalence thân in a random general population sample (*19,21*). This was also found among the miners and could not therefore be related to exposures in the smelter only.

Blood pressure (both systolic and diastolic) was found, as expected, to be significantly correlated with age in copper smelter employees and miners; the correlations were consistently higher in copper smelter employees. Significant correlations between blood pressure and Cd-U were found for the smelter workers; no such correlations were detected for miners (Table 21). A partial correlation analysis of blood pressure (systolic and diastolic) versus Cd-U, controlling for age, indicated that age accounted for the correlation between blood pressure and Cd-U in copper smelter workers.

The relative importance of several factors with potential contribution to hypertension was also investigated. These factors are: age, an index of body weight versus height (Quetelet Index), duration of employment in the smelter, cadmium absorption and body burden as reflected by Cd-B and Cd-U, and lead absorption as reflected by ZPP. Based on Mallows' $C_p$ Criterion, it was found that age and body weight had a greater contribution to hypertension than Cd-B, Cd-U and ZPP.

# Conclusion

Levels of lead, cadmium and arsenic absorption were assessed in this copper smelter work force. Significantly higher levels of Pb-B, ZPP, Cd-B, Cd-U and As-U, than in a group of miners without copper smelter experience, were documented. The degree of lead and cadmium absorption, as reflected in Pb-B, ZPP, Cd-B and Cd-U, was slight to moderate.

Renal function was not found to be affected to the extent it has been reported in other cadmium-exposed groups or to the degree found in our previous studies on other lead-exposed occupational groups. This is related to the relatively lower levels of absorption of both lead and cadmium in the copper smelter population studied. No additive or synergistic effect of absorption of these two nephrotoxic metals could be detected at these relatively low to moderate levels of cadmium and lead absorption.

Effects on systolic and diastolic blood pressure were also explored; no significant effect attributable to cadmium and/or lead absorption could be detected.

Mean, median and range of Pb-B, Cd-B and Cd-U for the major job classifications in the copper smelter indicated a rather marked gradient of exposure and absorption of Cd and Pb. Appropriate protective measures to reduce absorption in the highest ranking job classifications are indicated.

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## REFERENCES

1. Savoie, J.-Y., and Weber, J.-P. Étude de la distribution de certains toxiques dans la population de Rouyn-Noranda. Rapport Final, Principes d'Evaluation et de Controle des Effets sur la Santé du Fait des Contaminants de l'Environnement, Région Rouyn-Noranda, Bureau d'Étude sur les Substances Toxiques, Services de Protection de l'Environnement, Gouvernement du Québec, 1979.
2. Theriault, G., Cordier, S., and Iturra, H. Comportement de la mortalité dans la region de Rouyn-Noranda. Rapport Final, Region Rouyn-Noranda, Bureau d'Étude sur les Substances Toxiques, Services de Protection de l'Environnement, Gouvernement du Québec, 1979.
3. Fernandez, F. J. Micromethod for lead determination in whole blood by atomic absorption, with the use of graphite furnace. Clin. Chem. 21: 558–561 (1975).
4. Stoeppler, M., Backhaus, F., Dahl, R., Dumont, M., Hagedorn-Goetz, H., Hilpert, K., Klahre, P., Rutzel, H., Valenta, P., and Nurnberg, H. W. Determination of lead and cadmium in biological matrices. In: Proceedings International Symposium on Recent Advances in the Assessment of Health Effects of Environmental Pollution, Paris, France, June 24–28, 1974.
5. Eisinger, J., Blumberg, W. E., Fischbein, A., Lilis, R., and Selikoff, I. J. Zinc protoporphyrin in blood as a biological

indicator of chronic lead intoxication. J. Environ. Pathol. Toxicol. 1: 897–910 (1978).

6. Blumberg, W. E., Eisinger, J., Lamola, A. A., and Zuckerman, D. M. Zinc protoporphyrin level in blood determined by a portable hematofluorometer: a screening device for lead poisoning. J. Lab. Clin. Med. 89: 712–723 (1977).
7. Fischbein, A., Eisinger, J., and Blumberg, W. E. Zinc protoporphyrin determination: a rapid screening test for the detection of lead poisoning. Mt. Sinai J. Med. 43: 294–299 (1976).
8. Phadebas $\beta_2$ micro test. Pharmacia Diagnostics, AB, Uppsala, Sweden.
9. Gomez, M., Duffy, R., and Trivelli, V. At Work in Copper. Occupational Health and Safety in Copper Smelting. Inform Inc., New York, 1979.
10. Draper, N., and Smith, H. Applied Regression Analysis, 2nd ed. John Wiley and Sons, New York, 1981.
11. Friberg, L., and Vahter, M. Assessment of exposure to lead and cadmium through biological monitoring, results of a UNEP/WHO global study. Environ. Res. 30: 95–128 (1983).
12. Roels, H. A., Buchet, J.-P., Bernard, A., Hubermont, G., Lauwerys, R., and Masson, P. Investigations of factors influencing exposure and responses to lead, mercury, and cadmium in man and in animals. Environ. Health Perspect. 25: 91–96 (1978).
13. Bernard, A., Buchet, J.-P., Roels, H., Masson, P., and Lauwerys, R. Renal excretion of proteins and enzymes in workers exposed to cadmium. Eur. J. Clin. Invest. 9: 11–22 (1979).
14. Ellis, K. J., Vartsky, D., Zanzi, I., Cohn, S., and Yasumura, S. Cadmium: *in vivo* measurement in smokers and non-smokers. Science 205: 323–325 (1979).
15. Lauwerys, R. R., Roels, H., Buchet, J.-P., Bernard A., and Stanescu, D. Investigations on the lung and kidney function in workers exposed to cadmium. Environ. Health Perspect. 28: 137–145 (1979).
16. Wesson, L. G. Physiology of the Human Kidney. Grune and Stratton, New York, 1969, pp. 98–101, 633–635.
17. Brochner-Mortensen, J., Jenson, S., and Rodbro, P. Assessment of renal function from plasma creatinine in adult patients. Scand. J. Urol. Nephrol. 11: 263–270 (1977).
18. Lilis, R., Valciukas, J. A., Fischbein, A., Andrews, G., and Selikoff, I. J. Renal function impairment in secondary lead smelter workers: correlations with zinc protoporphyrin and blood lead levels. J. Environ. Pathol. Toxicol. 2: 1447–1474 (1979).
19. Lilis, R., Valciukas, J. A., Singer, R., Glickman, L., Kon, S., Sarkozi, L., Campbell, C., and Selikoff, I. J. Assessment of lead health hazards in a body shop of an automobile assembly plant. Am. J. Ind. Med. 3(1): 33–51 (1982).
20. Friberg, L., Kjellström, T., Nordberg, G., and Piscator, M. Cadmium. In: Handbook on the Toxicology of Metals (L. Friberg, G. Nordberg, and V. Vouk, Eds.), Elsevier-North Holland Biomedical Press, Amsterdam, 1979, pp. 255–387.
21. Selikoff, I. J., and Anderson, H. A. A survey of the general population of Michigan for health effects of polybrominated biphenyl exposure. Report to the Michigan Department of Health, 1979.